REMARKS

In the Final Office Action dated September 24, 2008, Claims 1-2, 5, 13, 15-17, 20, 28 and 30-31 were pending and under consideration. All pending claims were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner et al. (*Am. J. Pathol.* 146: 46-55, 1995) ("Greiner") in view of Nomoto et al. (*Clinical Cancer Res.* 8: 481-487, 2002) ("Nomoto").

This Response addresses the Examiner's rejection. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claim Amendments

Independent claims 1, 2 and 17 have been amended to delete references to the neoplastic conditions such as leukemia, lymphoma, and myeloma. The claims, as amended, are directed to the detection of clonal populations of non-neoplastic cells.

Claims 32 and 33 are added, which are supported by original claims 7 and 22.

No new matter is introduced by the foregoing amendments.

35 USC § 103(a)

The Examiner rejected the claimed subject matter as allegedly obvious over Greiner et al. (*Am. J. Pathol.* 146: 46-55, 1995) ("Greiner") in view of Nomoto et al. (*Clinical Cancer Res.* 8: 481-487, 2002) ("Nomoto").

The Examiner is of the opinion that Greiner teaches a method of detecting and monitoring a clonal population of cells in leukemia, e.g. acute lymphoblastic leukemia, in a denaturing gradient gel electrophoresis (DGGE) analysis which involves co-localization of nucleic acids derived from a subject. Greiner also allegedly teaches that co-localization higher than a background level is indicative of the presence of the clonal population.

The Examiner concedes that Greiner does not teach methods based on the detection of mitochondrial DNA (e.g. the D loop), but alleges that Nomoto supplements this deficiency. Nomoto allegedly teaches the analysis of the mitochondrial D loop to determine the clonality of hepatocellular carcinoma cells. Accordingly, the Examiner is of the view that it would have been *prima facie* obvious to one of skill in the art to have analyzed the polymorphic D loop sequences taught by Nomoto in an analysis of clonal populations of cells in acute lymphoblastic leukemia in accordance with the methods of Greiner.

In the first instance, Applicants observe that Greiner relates to an analysis of the clonality of tumor cells in leukemia/lymphoma patients using PCR and denaturing gradient gel electrophoresis, directed to analyzing TCR –γ gene rearrangements. It is believed that the Examiner has not appreciated the difference between analyzing rearranged T cell receptor DNA, versus germline DNA regions which do not undergo rearrangement in somatic cells. The TCR and immunoglobulin gene regions are unique, and not comparable to any other type of germline DNA present in a somatic cell, since they undergo rearrangement at the germline level subsequently to commitment of a cell to the T cell or B cell lineage. That is, the issue is not one of whether or not a particular region of DNA undergoes some level of germline changes, but rather the nature of that change. The type of change involved respecting the genes encoding the T cell receptor and the immunoglobulin molecule is unique in that the change takes the form of the rearrangement of sections of the germline DNA. However, the presently claimed invention is directed to analyzing DNA regions in which *acquired* mutations occur *at the time that the descendants of an ancestral cell divide to form new daughter cells.* The rearrangements that occur to the T cell receptor and immunoglobulin molecule DNA do not occur at this time. Rather, only after a cell has become committed to the T cell or B cell linage does it undergo

germline DNA rearrangement and thereafter all daughter cells express *the same* rearrangement pattern.

Therefore, Applicants respectfully submit that the TCR –γ gene rearrangement of Greiner is an entirely different type of cellular event, and one skilled in the art would simply not have combined the teaching of Greiner with an article such as Nomoto which, according to the Examiner, deals with the acquired DNA mutations of the mitochondrial DNA.

Nevertheless, without prejudice and in an effort to advance prosecution, Applicants have amended the claims such that they are directed to screening for non-neoplastic clonal populations. The cited references do not teach or suggest detection of non-neoplastic conditions. In fact, neoplastic conditions are so unique that it is counter-intuitive to assume that phenotypic or functional features of neoplastic cells would also be found in non-neoplastic cells.

In this regard, it is noted that Greiner relates to an analysis of the clonality of tumor cells in leukemia/lymphoma patients using PCR and denaturing gradient gel electrophoresis, directed to analyzing TCR –γ gene rearrangements. As discussed above, the screening of TCR rearrangements is irrelevant to the basis of the present invention. Nomoto relates to the determination of tumor clonality in patients with hepatocellular carcinoma by PCR analysis of D loop mitochondrial DNA mutations. Therefore, both of these articles relate to methods for detecting or monitoring the clonality of cells of a malignant neoplasm, as opposed to detection of clonality of non-neoplastic cells as presently claimed. Further, Greiner is even more removed from the claimed invention because this reference does not disclose or suggest the notion of acquired germline mutations in daughter cells. Moreover, as the Examiner has stated on page 7 of the Office Action, Nomoto offers "a general teaching that D loop mutations allow for the identification of the monoclonal origin of *tumor* tissue" (emphasis added). The tumor tissue

studied by Nomoto was a malignant solid cancer, namely, hepatocellular carcinoma. Nowhere does Nomoto teach or suggest that a method for analysis of mitochondrial D loop mutations in cells of patients with non-neoplastic conditions would be effective.

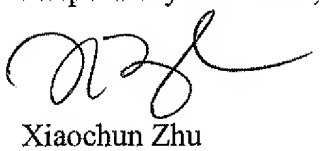
Therefore, even assuming, *pro arguendo*, Greiner and Nomoto had been combined, the claimed invention is still unobvious over the combination of the references.

Accordingly, the rejection under 35 U.S.C. §103(a) based on the combination of Greiner and Nomoto is overcome. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Xiaochun Zhu
Registration No. 56,311

Scully, Scott, Murphy & Presser, P. C.
400 Garden City Plaza-STE 300
Garden City, New York 11530
Telephone: 516-742-4343
XZ:ab/eh